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Concise Review

Reconsidering the "protective" theory of *Helicobacter pylori* infection in eosinophilic esophagitis

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Since its discovery, *Helicobacter pylori* (*H. pylori*) has found increasing attention in the biomedical world with its numerous pathophysiologic implications, both gastrointestinal and systemic. Beyond its well-established carcinogenic properties, emerging evidence also supports "harmful" proinflammatory and neurodegenerative roles of *H. pylori*. On the other hand, *H. pylori* infection has been proposed to be "protective" against several diseases, such as asthma and gastroesophageal reflux disease. Eosinophilic esophagitis (EoE) is a relatively new, allergen/immune–mediated disease, which has also been linked to these considerations. Main arguments are a postulated shift of immune responses by *H. pylori* from T helper 2 (T_H2) to T_H1 polarization, as well as a potential decline of the *H. pylori* burden with the dramatic parallel rise of EoE: a series of observational studies reported an inverse association. In this review, we counter these arguments by providing further epidemiological data, which point out that this generalization might be rather incomplete. We also discuss the limitations of the existing studies evaluating a possible association. Furthermore, we provide current evidence on common pathogenetic components, which share both entities. In summary, the claim that *H. pylori* is protective against EoE is rather incomplete and further mechanistic studies are necessary to elucidate a possible association.

Keywords: eosinophilic esophagitis; *Helicobacter pylori*; epidemiology; inflammation; microbiome

Introduction

Over the last decades, *Helicobacter pylori* (*H. pylori*) has attracted scientific interest with its pleiotropic manifestations; its demonstrated etiologic associations include chronic gastritis, peptic ulcer, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma.[1–4] Beyond the aforementioned substantiated pathogenicity of *H. pylori* locally in the stomach and duodenum, there have been emerging data supporting an extended impact on almost the entire gastrointestinal tract (GIT): growing evidence supports an association of *H. pylori* infection with colorectal neoplasms[5,6] and esophageal adenocarcinoma (EAC) in certain subpopulations.[7,8] Of note, *H. pylori* has been identified in the esophagus,[9–11] oral and nasal cavities,[12–14] and in normal and colorectal tumor tissues by the means of polymerase chain reaction or histology.[5,6,15] Moreover, a plethora of extragastric manifestations have been attributed to *H. pylori* infection. Clearly confirmed such manifestations include iron deficiency anemia, idiopathic thrombocytopenic purpura, vitamin B_{12} deficiency, and to a lesser extent, dermatological manifestations.[16] Additionally, such disorders include metabolic syndrome–related nonalcoholic fatty liver disease,[5,17–22] currently renamed to MAFLD (metabolic (dysfunction)–associated fatty liver disease),[23] and neurodegenerative diseases[16,24–26]; *H. pylori* infection has been linked with mild cognitive impairment, Alzheimer's disease (AD), multiple sclerosis, and primary

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open-angle glaucoma (defined as "ocular AD"), at least in certain ethnic subpopulations..[27–30] In summary, despite some controversy, an emerging number of publications supports the pleiotropic and beyond the stomach/GIT pathogenicity of *H. pylori.*

Eosinophilic esophagitis (EoE) is a rather new, moderately well-comprehended disease,[31] first described in 1993 by Attwood *et al.*[32] and in 1994 by Straumann *et al.*[33] It is defined as an allergen/immune–mediated entity with the symptoms of esophageal dysfunction, most commonly food impaction, and eosinophilic infiltration of the esophageal mucosa (more than 15 eosinophils per high-power field) in the absence of secondary causes of eosinophilia.[34] Specifically, EoE, representing a principal cause of upper gastrointestinal (UGI) morbidity, is ranking as the second most common chronic esophageal disease and the leading etiology of esophageal food impaction and dysphagia in both children and young adults.[34–36] The natural history of EoE suggests an advancement of the disease over time, where tissue remodeling takes place, transiting the initially inflammatory phenotype to a fibrostenotic one.[37,38] Since there are several reports of a rapid increase of EoE prevalence[34,37,39] and its pathogenicity is only partly unraveled, it is of particular interest to develop novel therapies and strategies, which might change this course and provide an early relief in affected patients. In this regard, emerging evidence proposed a "protective" effect of *H. pylori* infection on EoE or at least a negative association. Likewise, *H. pylori* has been linked in the past to a "protective" effect of other allergic or nonallergic entities.

The aim of our review was to present current evidence regarding the "protective" effect of *H. pylori* on EoE and propose another critical point of view with further evidence, which counters this protective consideration. Thus, the former conventional approach may not reflect the whole truth and possibly represents only one side of the coin. Moreover, potential common pathogenic components of both diseases are reviewed, which might trigger future mechanistic studies that will further elucidate their possible association.

"Protective" theory

Despite the fact that *H. pylori* was officially classified by the World Health Organization as a definite (or so-called class I) carcinogen[40] as early as in 1994, the statement that was later reconfirmed in 2012,[41] an increasing number of studies began to spread the speculation of *H. pylori* possessing "protective" properties in the late 1990s.[42–45] Typical diseases that have been associated with a beneficial, "protective" role of *H. pylori* infection include, among others, inflammatory bowel disease,[46] asthma,[47,48] and gastroesophageal reflux disease (GERD).[49–52] Regarding the disease of interest, EoE, the first study that described an inverse association dates back to 2003; Cheung *et al.*[53] reported the lower rates of *H. pylori* infection in Australian pediatric patients with esophageal eosinophilia (EoE) compared with the control group.[53] Four years later, Ronkainen *et al.*[54] revealed that Swedish adult EoE patients were also characterized by less severe *H. pylori* infection than their control counterparts, thus giving rise to suggestions of a "protective" effect in the relevant studies later.[55–60]

A "protective" effect of *H. pylori* has been also attributed to other than EoE allergic diseases, for instance, for asthma, with the argument that a percentage of asthmatic patients may be associated with GERD and *H. pylori* eradication may also deteriorate GERD. The potential "protective" role of *H. pylori* is consistent with the so-called "hygiene hypothesis," that namely, microbial infections during early childhood might be preventive or eliminate asthma and other allergic conditions.[47]

However, conflicting data are also reported.[61,62] Malaysian people, for example, who are characterized by a low prevalence of *H. pylori* infection also exhibit a low incidence of childhood asthma, GERD, Barrett's esophagus (BE), and distal esophageal cancers, which would indicate that in this population, *H. pylori* infection is not needed as a "protective" factor against the above-mentioned conditions.[63] A recent study with an animal model of asthma showed that the extract of *H. pylori* improved parameters of respiratory inflammation and goblet cell hyperplasia after repeated allergen exposure.[64]

Regarding GERD, there is accumulating evidence supporting the sequence GERD–BE–EAC and *H. pylori* implication separately in each single step to EAC, at least in certain populations.[65,66] A large-scale study (20,918 cases)[67] reported that the reduction in *H. pylori* infection parallels the decline in peptic ulcer prevalence, and that the rise in GERD and/or the reappearance of GERD follow-

Q2

ing *H. pylori* therapy is rare. Likewise, contrary to expectations, another large-scale study with 61,548 in-patient cases with duodenal ulcers apparently attributed to *H. pylori* infection had a 70% increased risk of GERD-related EAC complication.[68]

In addition, *H. pylori* infection influences the gastrointestinal (GI) microbiome composition including species of the stomach, such as *Campylobacter* spp. *H. pylori* infection promotes the gastric microbiota dysbiosis, which might contribute to EAC as implied by the high concentrations of *Campylobacter* species in the BE biofilm and the predominance of Gram-negative bacteria.[7]

In summary, these data might indicate the notion that *H. pylori* is not protective against any diseases, including GERD, and its related complications, including BE and EAC.[69]

Interestingly, atopic pathologies, including asthma and EoE, consist of frequent comorbidities in patients with GERD, though in each disorder, the indication of an etiologic link is uncertain.[70] In the pediatric population, the highest ranking EoE comorbidities include asthma (13.4%), GI diseases (7.26%), allergies (7.01%), and GERD (3.69%).[71] Moreover, in adult patients with GERD refractory to treatment, the prevalence of EoE is 9.7%[72]

H. pylori and EoE: illuminating the gap

The current global prevalence of *H. pylori* infection seems to be higher than that of EoE. Its prevalence is about 58% (varying from 39.9% to 91.7%).[7,73] Likewise, there has been noticed a remarkable increase in the incidence of EoE in the last two decades, constituting EoE nowadays as a major etiology of UGI morbidity.[35,37] According to the recent data, a global average EoE incidence is 3.7/100,000 per year, with variations ranging from 2.1/100,000 per year in the Netherlands to 12.8/100,000 per year in the United States (Ohio).[37] EoE is also detected in 1–8% of symptomatic patients undergoing endoscopy,[37] whereas, for instance, comparable recent features of *H. pylori* infection are higher (41–63.67%).[74,75] Moreover, the current prevalence of *H. pylori* infection in Asia is: Central Asia 79.5%, South Asia 28.6–81%, and Western Asia 49.1–77.2%.[76] Additionally, owing to immigration, *H. pylori* infection prevalence in Western countries is high. When compared with the indigenous populations, immigrants and refugees living in Western countries frequently exhibit high rates (72–93%) of *H. pylori* infection.[7,77,78] Furthermore, for example, in Asia, *H. pylori* infection prevalence is 44.4–54.0% among patients with GERD.[79] By contrast, for example, EoE is uncommon in Singapore[80]; in South Asia, EoE prevalence is only 3.2% among patients with symptoms suggestive for GERD[81] or it exhibits a rising trend[82]; and in East Asia, EoE prevalence is 9.7% among adult patients with GERD refractory to treatment.[72] Moreover, in the United States, the mentioned EoE pediatric population exhibit GERD at a rate of 3.69%.[71]

Therefore, these data indicate that the conventional claim that declining *H. pylori* prevalence has led to a rise of allergic and immune-mediated inflammatory diseases, including EoE, needs to be better studied.

Although EoE pathophysiology is not fully elucidated yet, it implicates a plethora of contributing factors, mainly immunogenetic and environmental ones.[38,83–85] Among the variety of environmental factors that have been studied for a potential contribution to EoE, emerging evidence reveals the role of microbial imbalance, particularly of intestinal imbalance, in EoE pathogenesis.[38] For instance, cesarean section and antibiotic exposure of infants predispose them to the onset of EoE. Moreover, as in the case of the aforementioned *H. pylori* infection–induced microbiota dysbiosis accompanied by the high concentrations of *Campylobacter* spp. in the BE biofilm,[7] the ingestion of known EoE-triggering foods can lead to an imbalance of the esophageal microbiota, with the emergence of *Campylobacter* and *Granulicatella* genera on mucosal biopsies.[38] Specifically, the accumulating data indicate a role of bacteria in the complex pathophysiology of EoE; the esophageal microbiota, a rich environment consisting of varied bacterial species, is critically changed by inflammation, including EoE; and some pathogens have been proposed as risk factors, while others exhibit protective effects on EoE pathogenesis.[86–88]

Focusing on the investigation between *H. pylori* infection and EoE,[53–60,89,90] the majority of clinical studies reported an inverse association attributing "protective" properties to *H. pylori* infection against EoE, while some recent multicenter research failed to show such a negative correlation (Table 1).[91] Of note, the latter authors previously claimed that the inverse association between *H. pylori* and EoE might only represent an epiphenomenon as part of

Table 1. Summary of all available studies having evaluated the possible association between *H. pylori* infection and EoE or EE Q3

Refs.	Country period	Design/ diagnosis	Case numbers (EoE(EE)/ CG) and age group	EoE (EE) definition	CG definition	Endoscopic documentation	CG biop-sies	Previous *H. pylori*/ EoE treatment	*H. pylori* prevalence (EoE/CG), %	OR (95% CI)/ P value
53	Australia 1989–2000	RSC/NA	21/21 Pediatric	Dysphagia and > 20 Eos/HPF	Dysphagia and < 5 Eos/HPF	Specimens of the lower esophagus, stomach (corpus and antrum), and duodenum (third part)	Yes	NA/NA	4.8/9.5	NA
54	Sweden 1998	PSC/ histology and culture	48(EE)/952 Adult	EoE (D) ⩾20 Eos/HPF EoE (P) ⩾15–19 Eos/HPF EoE (Po) 5–14 Eos/HPF "Eos present" 1–4 Eos/HPF	0 Eos/HPF	≥2 biopsies ((above) Z-line, pathologic areas)	Yes	NA/NA	1.7/34.8	$P = 0.04$
59	The United States 2008–2010	PMC/ histology	5767 (EE), 2367 (EoE)/56,30 Mixed	EE; any Eo and EoE sensitivity analysis with nested categories ≥15, ≥45, ≥75, and ≥90 Eos/HPF	Normal biopsies without Eos infiltration	Esophageal and gastric biopsies	Yes	NA/NA	5.7 (EE) 5.1/7.2	0.69 (0.77–0.87)
90	The United States NA	PSC/ histology	33 (EE)/ 1324 Adult	EE: >15 Eos/HPF; EoE (D): esophageal symptoms and antacids EoE (P): EE and esophageal symptoms or antacids and EE	<15 Eos/HPF	≥1 esophageal biopsy 2–3 cm above the normal SCJ, and biopsies from suspected BE and multiple gastric biopsies	Yes	Variable/ variable	9.7/22.8	$P = 0.08$
55	Japan 2010–2011	RSC/ IgG serology	18/54 NA	Esophageal dysfunction and >15 Eos/HPF	Healthy individuals at the annual check-up without EoE history	NA	No	NA/NA	22.6/55.6	0.22 (NA)
58	The United States 2007–2012	RSC/ histology and RUT	62/904 Pediatric	≥15 Eos/HPF	<15 Eos/HPF	Esophageal biopsies (if EoE suspicion 3 + 3 (distal/proximal), when EoE was suspected); gastric (antrum, four for histology; two for RUT; and two for the corpus); two from the duodenal bulb, and two from the second part of the duodenum	Yes	NA/PPI failure	1.6/3.9	0.096 (0.013–0.72)
89	China NA	Prospective population-based study/IgG serology	67 (EE)/954 Adult	EE: any eosinophilia EoE: ≥15 Eos/HPF	0 Eos/HPF	≥4 biopsies above Z-line and any pathologic areas	No	NA/NA	68.7/72	0.85 (0.49–1.45)
56	Germany NA	RSC/IgG serology	58/116 Adult	Esophageal symptomatology and >15 Eos/HPF	Healthy individuals without EoE	Two esophageal biopsies above the GEJ and two proximal	No	NA for control group/NA	13.8/37.9	0.24 (0.11–0.50)

Continued

Table 1. ***Continued***

Refs.	Country period	Design/ diagnosis	Case numbers (EoE(EE)/ CG) and age group	EoE (EE) definition	CG definition	Endoscopic documentation	CG biop-sies	Previous *H. pylori*/ EoE treatment	*H. pylori* prevalence (EoE/CG), %	OR (95% CI)/ P value
57	The United States 2008–2015	RMC/ histology	25,969/ 284,552 Mixed	Three criteria 1. Dysphagia and >-15 Eos/HPF 2. Dysphagia and exclusion of other causes[a] and >-15 Eos/HPF 3. >50 Eos/HPF and exclusion of other causes[a]	Absence of histologic findings	Gastric–esophageal biopsies	Yes	NA/NA	4.5/7.3	0.77 (0.73–0.8)
60	Sweden 2009–2014	PSC/RUT	9/14 Adult	Esophageal dysfunction and ≥15 Eos/HPF	GERD and < 15 Eos/HPF	Diagnostic biopsies, two bacterial samples above the Z-line, biopsies repeated at the proximal esophagus 5 cm below the UES, and brush samples as well as two biopsies from the buccal mucosa	Yes	NA/2 weeks without PPI before biopsy	0/14.3	NA
91	Spain Italy France Colombia 2014–2017	PMC/ histology, UBT, RUT, and stool Ag	404/404 Mixed	Esophageal symptomato-logy and ≥15 Eos/HPF	Esophageal symptoms and <-5 Eos/HPF	≥6 esophageal biopsies	Yes	Naive/naive	37.4/39.3	0.97 (0.73–1.30)

Ag, antigen; CG, control group; CI, confidence interval; BE, Barrett esophagus; EE, esophageal eosinophilia; EoE, eosinophilic esophagitis; Eos, eosinophils; GEJ, gastroesophageal junction; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; HPF, high-power field; Ig, immunoglobulin; NA, not available; OR, odds ratio; PMC, prospective multicenter; PPI, proton pump inhibitor; PSC, prospective single center; RMC, retrospective multicenter; RSC, retrospective single center; RUT, rapid urease test; SCJ, squamocolumnar junction; UBT, urea breath test; UES, upper esophageal sphincter.

[a]Gastroesophageal reflux esophagitis, Barrett esophagus, eosinophilic gastroenteritis, inflammatory bowel disease, or other etiologies for eosinophilia, (D), definite, (Po), possible, (P), probable.

a more general change in human microecology.[92] Other experts also share the same point of view.[93]

Moreover, it has been repeatedly investigated, whether there is an association between *H. pylori* infection and EoE[37,38,94–96]; the majority of clinical studies[53–60] report an inverse association or "negative correlation." However, the aforementioned case–control studies are characterized by multiple methodological limitations (Table 1), which may confine the interpretability or even dispute their results.[91] For instance, the two largest studies performed by the same coauthors[57,59] were of retrospective nature. Moreover, the protocol for obtaining gastric mucosa biopsy specimens was not provided[59] (or mentioned that only 3.9% of biopsy sets were compliant with the Sydney System[57]) and no additional data regarding previous proton pump inhibitor (PPI) discontinuation before biopsies were available. These data about PPI withdrawal were not provided in another study, which also used histology as a diagnostic modality.[58] Therefore, concerns have been raised about false-negative *H. pylori* status in these studies. In the first large studies,[54,59] EoE cases have been identified by any EoE, without taking into account the histological cutoff of 15 eosinophils per high-power field. Besides, data in regard to previous eradication regimens[54,56–59] or esophageal symptoms[54,56–59] were absent or incomplete in some patients. As far as the prospective study of Ma *et al.*[89] is concerned, the small sample size, the usage of serology as a diagnostic modality for *H. pylori infection,* and the lack of esophageal biopsies in the control group question the reported results. It needs to be

emphasized that serology (IgG anti-*H. pylori* antibodies) cannot discriminate between active or previous *H. pylori infection*, and this may lead to a substantial number of false-positive results. Noteworthy is also the point that the majority of these studies found a surprisingly extremely low prevalence of *H. pylori* infection[53,57–60] in both control and EoE groups (Table 1). Of note, a recent comprehensive systemic review and meta-analysis assessed the global prevalence of *H. pylori infection*; The lowest *H. pylori* prevalence rates were found in Switzerland (18.9%), Denmark (22.1%), New Zealand (24.0%), Australia (24.6%), and Sweden (26.2%).[76] Even these lowest rates are five to ten times higher than the estimated *H. pylori* prevalence in the four previous case–control studies.[57–60] In the only large prospective (808 individuals) and multicenter (23 centers) study,[91] where these limitations from previous case–control studies were taken into account, no inverse association was reported between *H. pylori* infection and EoE; no significant difference in the prevalence of *H. pylori* infection was recognized between cases and controls in both children (42% versus 46%) and adults (38% versus 38%). A borderline inverse association could be verified for allergic rhinitis and atopy, but not for food allergy or even asthma. These findings questioned the protective role of *H. pylori* infection against allergic pathologies, including EoE. A second earlier study[90] with prospective design and *H. pylori* diagnosis based on histology failed to show statistical significance for *H. pylori* infection between EoE and control groups (Table 1). Interestingly, similar further results have been shown by other research groups, which claimed conflicting inverse or positive associations depending on either the socioeconomic environment or national descent, pointing at the existence of potentially not considered confounders, which might, however, influence this association.[97,98]

Two major arguments of the supporters of the protective *H. pylori* viewpoint are the following: (1) the bacterium shapes a T_H1 immune response, whereas EoE as an allergic reaction is classically T_H2-polarized, and (2) the already criticized consideration that the increase of EoE prevalence/incidence is correlated with a currently undocumented rapid decrease in *H. pylori* prevalence over the past several decades, which matches the increase in EoE prevalence.[37,38,83] These claims seem to be incomplete and represent only one side of the coin.

It is recognized that *H. pylori* infection does not induce a pure T_H1-polarized immune response, but rather a mixed, T_H1/T_H17 predominant response[99]; it also induces the differentiation of anti-inflammatory T_H2 cells.[4,100] Additionally, EoE patients with the late-onset and more intense allergic inflammation are characterized by a mixed T_H1 and T_H17 cytokine milieu for supporting the development of T_H interleukin (IL)-17 positive cells.[101] In a recent EoE study with pediatric and adult cases, it was demonstrated that T_H17 cells have a role in EoE pathogenesis.[102]

Concerning the second epidemiological argumentation of "protective" *H. pylori* supporters, it may be only a coincidental event without, an etiologic association. In this respect, for example, it has to be acknowledged that recent studies also do exist reporting no statistically significant difference in incidence rates of EoE by year[103]; nevertheless, there was a significantly lower incidence rate in individuals aged less than 16 compared with those aged 16 or more. Moreover, a Mexican study that included adult patients with esophageal food impaction reported low prevalence (11.7%) of biopsy-proven EoE, whereas peptic stenosis was identified as the most common etiology.[104]

These data, despite the several methodological concerns, which confine interpretability (among others retrospective design, various bias or inability to rule-out GERD), are in contrast to previous reports of increasing prevalence rates and might reflect a leveling off of EoE prevalence.

Further evidence has accumulated with the elapse of time for both entities, which propose independently, that both EoE and *H. pylori* infection share common pathogenetic components (Fig. 1).

Galectins represent one typical paradigm; they belong to the lectin superfamily, a group of endogenous glycan-binding proteins, which can interact with glycosylated receptors expressed by a plethora of immune cells.[105] Galectin (Gal)-3 plays a role in *H. pylori* colonization of the gastric mucosa, as well as in the local immune response and chronic gastric implications.[106] Gal-3 might constitute an essential host factor for keeping *H. pylori* infection and colonization at subclinical levels. *H. pylori*–related Gal-3 also contributes to chronic cardiovascular, kidney, and brain disorders in

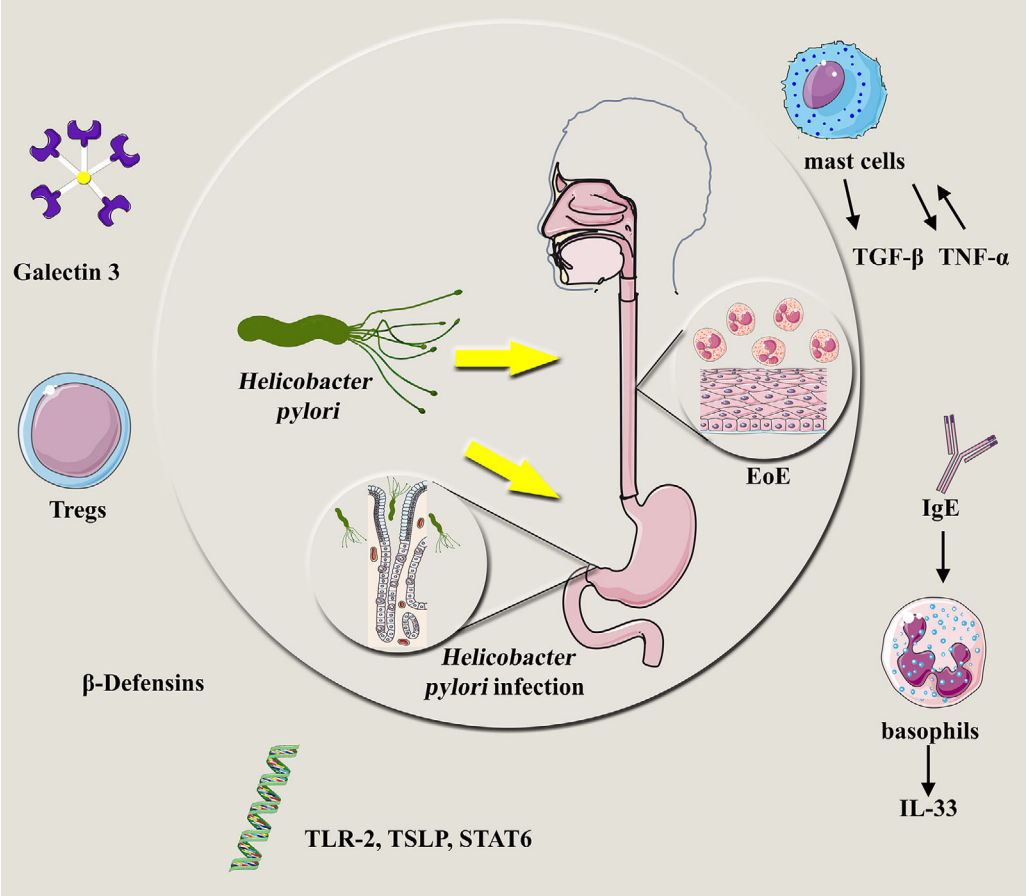

Figure 1. Proposed common pathogenetic components between *Helicobacter pylori* infection and eosinophilic esophagitis. EoE, eosinophilic esophagitis; Ig, immunoglobulin; IL, interleukin, STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TLR, Toll-like receptors; TNF, tumor necrosis factor; T_{regs}, regulatory T cells, TSLP, thymic stromal lymphopoietin.

decompensated cirrhosis.[107] In addition, Gal-3 plays a crucial proinflammatory role in allergic asthma by promoting eosinophil migration and trafficking[108]; Gal-3 is upregulated during allergic inflammatory response in atopic dermatitis.[109] In respect to other than EoE allergic diseases, which are IgE-dependent, it has also been reported *in vitro* Gal-3 to be essential for IgE-dependent activation of human basophils.[110] The last granulocyte population is a recognized immune cell type implicated in both *H. pylori* infection virulence and EoE pathogenicity.[38,111] Moreover, a proteomic analysis of the esophageal mucosa in patients with EoE showed a distinct abundance and nitrosylation profile, most remarkably in distal biopsies.[112] Gal-3 expression and S-nitrosylation were upregulated, which might explain a probable role in mucosal inflammation, and thus further research is needed to reveal in-depth the possible involvement of *H. pylori*–related Gal-3 in EoE pathophysiology.

Another aspect of EoE pathogenesis includes the mast cell population actively involved in the development of EoE.[113,114] Mast cells may promote inflammation and fibrosis in EoE, by secreting factors, such as transforming growth factor (TGF)-β, a proinflammatory cytokine that induces smooth muscle contractility contributing to esophageal dysfunction and tryptase, which promotes proliferation and collagen secretion.[84,115] Beyond EoE, TGF-β seems to be a substantial mediator in *H. pylori* infection pathogenesis.[116] TGF-β–inducing protein of *H. pylori* may mediate the immune response

and contribute to the pathogenesis of *H. pylori* infection.[117] Additionally, *H. pylori*–induced cytotoxin VacA exhibits chemotactic activities to the bone marrow–derived mast cells (BMDMCs) and induces BMDMCs for the production of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, which has been reported to be overexpressed in esophageal epithelial cells of EoE.[118,119] Of note, TNF-α is known for its ability to stimulate mast cells.[120,121] Moreover, IL-33 is a proapoptotic molecule, which is upregulated in active EoE.[38,101] IL-33 mRNA from the gastric epithelium and protein expression was also increased in both mice and human patients with *H. pylori infection*, which was positively associated with the bacterial load and the degree of gastritis.[122] IL-33 production was promoted via extracellular signal–regulated kinase signaling pathway activation by gastric epithelial cells in a cagA-dependent manner during *H. pylori infection*, which resulted in increased inflammation and bacterial burden within the gastric epithelium. Therefore, *H. pylori*–related mast cell–related TGF-β, TNF-α, and/or IL-33 might also contribute to the pathophysiology of EoE, and thus further research is needed to elucidate this field.

A further type of granulocyte polymorphonuclear cells with a special interest in EoE are basophils.[38] Several studies have emphasized the crucial role of basophils in allergic diseases including EoE; they may play a role in the complex pathophysiology of EoE.[123] In murine models of EoE, allergic skin sensitization promoted EoE via the IL-33–basophil axis.[124] The gastric mucosa of *H. pylori–infected* patients (affected by moderate and severe gastritis) is also infiltrated by basophils, and *H. pylori*–derived peptide (*H. pylori* (2–20)) appears to be a potent basophil chemoattractant.[111] The potential role of *H. pylori* (2–20) basophil chemoattractant, however, in the pathogenesis of EoE remains to be elucidated.

Regulatory T cells (T_{reg}) play a compelling role in the pathophysiology of EoE. Regarding *H. pylori infection*, some data indicate that both T_H1 and T_H17 cells could be protective or pathogenic, whereas T_{reg} and T_H2 cells achieve anti-inflammatory impacts during *H. pylori* infection.[125] In a pediatric study, an increased number of infiltrating T_{reg} positive for forkhead box P3 (FoxP3) has been reported in esophageal biopsies of EoE patients.[126] Likewise, an increased number of FoxP3-positive T_{reg} was reported in *H. pylori*–positive gastritis.[127] However, the potential role of *H. pylori*–related T_{reg} in the pathophysiology of EoE remains to be defined.

Other molecules of interest are the antimicrobial peptides, defensins. Changes in the level of human β-defensins (hBDs) and other antimicrobial peptides are connected with various inflammatory and allergic diseases, such as asthma, thereby leading to novel treatments for many allergic diseases.[128] The diminished esophageal expression of hBD1 and hBD3 was reported in EoE, deducing that it might render the esophageal mucosa more susceptible to the onset or progression of EoE.[129] Likewise, *H. pylori* induces defensin release linked with chronic inflammatory tissue damage, while *H. pylori* can evade the attack by defensins[130]; human defensins may also play a role in *H. pylori*–related neurodegenerative disorders.[130,131] A potential impact of *H. pylori*–related inappropriate defensin expression in EoE pathogenesis remains to be clarified.

With respect to aforementioned *H. pylori*–related neurodegenerative and the rest of the extragastric pathologies, where *H. pylori* serves as a common denominator, two observations appear to be of interest for EoE: (1) although EoE is uncommon in elderly patients who exhibit dementia indices, it often leads to clinically overt dysphagia.[132] In this regard, *H. pylori*–related apolipoprotein E (ApoE)-4 polymorphism, the most common known genetic risk factor for AD onset, could be connected with dysphagic symptoms in such elderly patients; an association between *H. pylori* infection and ApoE4 polymorphism contributes to the pathogenesis of AD and, possibly, of glaucoma.[133] (2) MAFLD (where the evidence of *H. pylori* infection as the contributor accumulates[5,17–22]) and EoE seem to be the common topic in pediatric gastroenterology.[134]

Lastly, the genetic factors are linked with EoE.[38,83] Genes that contribute to EoE progression include calpain 14 (*CAPN14*), Toll-like receptors (*TLR*), *TSLP*, *EMSY* (or GL002, C11orf30), leucine-rich repeat containing 32 (*LRRC32*), *STAT6*, and the ankyrin repeat domain 27 (*ANKRD27*).[38,135] Some of the aforementioned genes, such as *TLR2, TSLP,* and *STAT6*, have also been linked with *H. pylori* infection.[136–140] A possible role of these *H. pylori*–related genes in EoE pathogenesis remains to be clarified.

Conclusion

H. pylori displays a wide spectrum of pathogenicity and many intriguing extragastric manifestations. The claim that *H. pylori* protects from EoE seems rather incomplete. Mechanistic studies in both human patients and animal models mimicking EoE investigating the aforementioned commonalities between two entities will elucidate pathogenic pathways and unravel new promising therapies.

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Author contributions

M.D. reviewed the literature and drafted the paper. J.K. and G.R. critically reviewed and revised the paper for important intellectual content.

Competing interests

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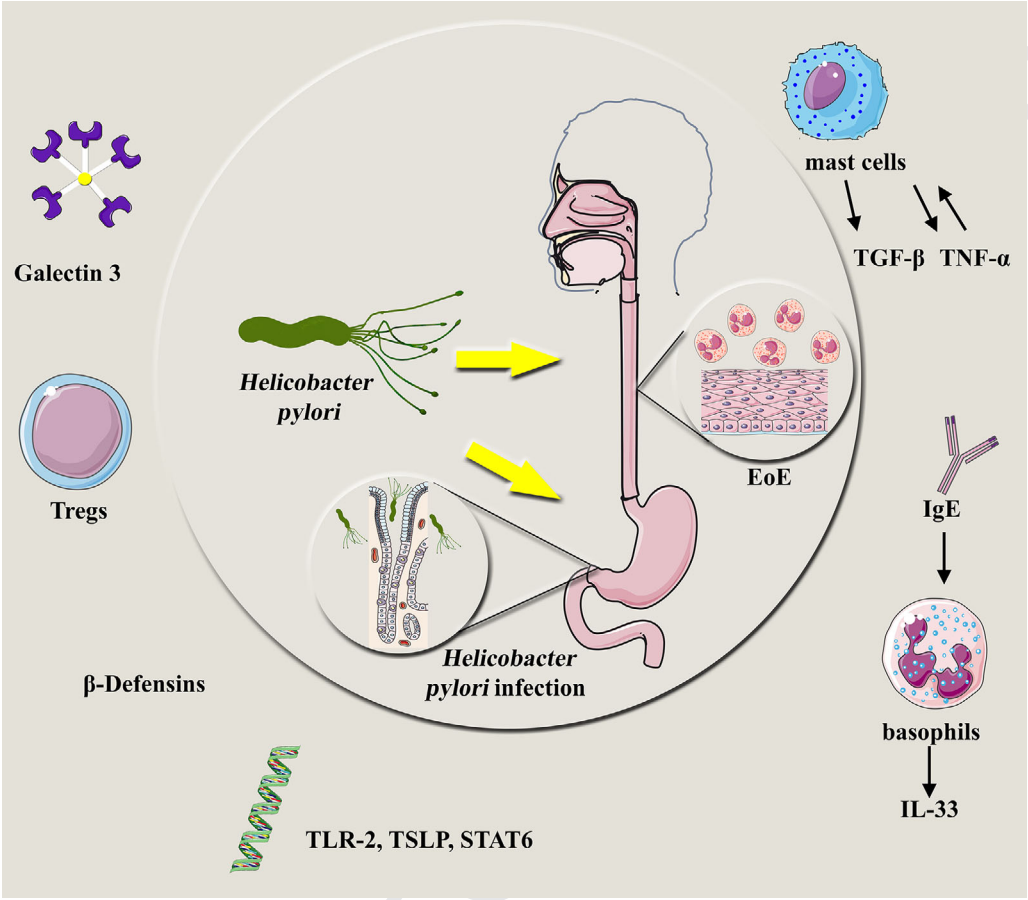
Graphical Abstract & Image



The aim of our review was to present current evidence regarding the "protective" effect of *H. pylori* on EoE and propose another critical point of view with further evidence, which counters this protective consideration. Thus, the former conventional approach may not reflect the whole truth and possibly represents only one side of the coin. Moreover, potential common pathogenic components of both diseases are reviewed, which might trigger future mechanistic studies that will further elucidate their possible association.